Synaptic mechanisms underlying thalamic activation-induced plasticity in the rat auditory cortex

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Zhu ZR, Xu F, Ji WG, Ren SC, Chen F, Chen PZ, Jiang HH, Mi Z, Hu B, Zhang J, Xiong Y. Synaptic mechanisms underlying thalamic activation-induced plasticity in the rat auditory cortex. J Neurophysiol 111: 1746–1758, 2014. First published February 5, 2014; doi:10.1152/jn.00180.2013.—Electrical stimulation of ventral division of medial geniculate body (MGBv) neurons evokes a shift of the frequency-tuning curves of auditory cortical (AC) neurons toward the best frequency (BF) of the stimulated MGBv neurons (frequency-specific plasticity). The shift of BF is induced by inhibition of responses at the BF of the recorded AC neuron, with coincident facilitation of responses at the BF of the stimulated MGBv neuron. However, the synaptic mechanisms are not yet understood. We hypothesize that activation of thalamocortical synaptic transmission and receptor function may contribute to MGBv stimulation-induced frequency-specific auditory plasticity and the shift of BF. To test this hypothesis, we measured changes in the excitatory postsynaptic currents in pyramidal neurons of layer III/IV in the auditory cortex following high-frequency stimulation (HFS) of the MGBv, using whole cell recordings in an auditory thalamocortical slice. Our data showed that in response to the HFS of the MGBv, the excitatory postsynaptic currents of AC neurons showed long-term bidirectional synaptic plasticity and long-term potentiation and depression. Pharmacological studies indicated that the long-term synaptic plasticity was induced through the activation of different sets of N-methyl-D-aspartate-type glutamatergic receptors, γ-aminobutyric acid-type receptors, and type 5 metabotropic glutamate receptors. Our data further demonstrated that blocking of different receptors with specific antagonists significantly inhibited MGBv stimulation-induced long-term plasticity as well as the shift of BF. These data indicate that these receptors have an important role in mediating frequency-specific auditory cortical plasticity.

The mammalian sensory cortex has a considerable capacity to adapt to changing environments (Beaulieu and Cyndar 1990; Coq and Xerri 1998; Weinberger 2007). The auditory cortical (AC) area devoted to sound frequency is not immutable and can be changed by behavioral training, environmental changes, and sensory deprivation. The capacity of the auditory cortex to change its response properties is known as “AC cortical plasticity” (Norena et al. 2006; Weinberger et al. 1990). Owl monkeys that had been trained over several weeks to discriminate sounds significantly expanded the cortical area tuned to the frequencies of the training tones (Recanzone et al. 1993). In addition to experience-induced neural plasticity, changes in the neuronal receptive fields of the auditory cortex can be induced by electrical stimulation of the ventral division of the medial geniculate body (MGBv) (Jafari et al. 2007; Ma and Suga 2009). The neuronal receptive fields in the auditory cortex change reliably toward the receptive fields of the electrically stimulated thalamic neurons, indicating the involvement of thalamocortical (TC) frequency-specific plasticity. Such receptive field changes can last for weeks.

Cortical receptive fields are formed by organized arrays of TC afferents that project onto neurons in the thalamorecipient layer III/IV of the auditory cortex as well as intracortical connections. Sound information is transmitted from the thalamus to the auditory cortex via TC afferents (Feldman and Brecht 2005; Liu et al. 2007). Studies have revealed that TC projections link those MGBv and AC neurons that have a similar characteristic frequency, which suggests that TC input directly mediates cortical response to characteristic frequency (Miller et al. 2001). It is thus likely that TC projections provide an anatomic basis for the plasticity of cortical neurons. In addition, several studies have shown that synaptic plasticity drives cortical map reorganization (Allen et al. 2003; Buonomano and Merzenich 1998; Feldman 2009). Long-term potentiation (LTP) and long-term depression (LTD), two fundamental forms of synaptic plasticity, can be induced in TC synapses (Feldman 2009; MacDonald et al. 2006; Malenka and Bear 2004). The importance of TC LTP and LTD in experience-dependent cortical plasticity and cortical map reorganization has been proven (Gagolewicz and Dringenberg 2011; Hardingham et al. 2003; Liu et al. 2013). However, different stimulation protocols are usually employed to induce LTP and LTD (Habib and Dringenberg 2010). We recently investigated the possibility of coexistence of LTP and LTD in AC neurons upon stimulation of the MGBv, using the same high-frequency stimulation (HFS) protocol described in the present study (Zhu et al. 2013). Our choice of HFS parameters is based on previously established work (Cai et al. 2013; Duffy and Nguyen 2003). Specifically, we have demonstrated that HFS of the MGBv produces both LTP and LTD as well as the shift of best frequency (BF) in AC neurons. The evoked potentiation and depression depended on the frequency of the electrical stimulation of the MGBv, correlated with the BF of MGBv, and AC neurons, respectively. However, the underlying synaptic mechanisms are still not known.

To this purpose, we made whole cell patch-clamp recordings of the synaptic plasticity in AC pyramidal neurons of layer III/IV after HFS of MGBv neurons in a TC slice preparation.
Our results indicate that HFS of thalamic neurons induces different forms of long-term synaptic plasticity (rapid and slow LTP/LTD), which involve activation of different sets of glutamergic, γ-aminobutyric acid (GABA)ergic, or endocannabinoid (eCB) receptors. Inhibition of these receptors prevented the induction of TC plasticity as well as the shift of BF in AC neurons, implying the essential role of receptor activity in mediating TC frequency-specific plasticity in the rat auditory cortex.

MATERIALS AND METHODS

Thalamocortical Slice Preparation and Maintenance

Sprague-Dawley rats (P21–28) were used in this study. Animals were obtained from the Laboratory Animal Center at the Third Military Medical University in China, and all protocols and procedures were approved by the University Animal Care and Use Committee. Acute primary TC slices containing the auditory cortex and portions of the MGB, in the thalamus were prepared as described by Cruikshank et al. (2002). After halothane anesthesia, each animal was decapitated and the brain was removed quickly. The brain was subsequently submerged in cold artificial cerebrospinal fluid (ACSF) containing (in mM) 125.0 NaCl, 2.5 KCl, 25.0 NaHCO3, 1.25 KH2PO4, 1.2 MgSO4, 2.0 CaCl2, and 10.0 dextrose, bubbled with 95% O2-5% CO2 with a pH of 7.4. The brain was blocked, and an oscillating tissue slicer (VT1000, Leica, Wetzlar, Germany) was used to cut 50-μm-thick sections. Sections were obtained from the left hemisphere by using a slicing angle of 15°. Slices were initially incubated for a minimum of 90 min at room temperature (22–24°C) in ACSF and were then transferred to and submerged in a recording chamber, where they were perfused continuously with oxygenated ACSF at room temperature.

Electrophysiological Recording and Stimulation

Whole cell patch-clamp recordings were obtained from cell bodies of layer III/IV thalamocerebral neurons in the rat auditory cortex. Pyramidal neurons are the principal thalamocerebral neurons in the thalamocerebral layers in the auditory cortex of many mammalian species (Richardson et al. 2009; Smith and Populin 2001). The cell bodies of these neurons were found with an upright microscope equipped with Leica differential interference contrast optics, a ×40 water immersion objective, and an infrared video imaging camera. Data acquisition was conducted with Axopatch 200B (Axon Instruments, Union City, CA) or EPC10 amplifiers (HEKA Elektronik, Lambrecht/Pfalz, Germany). The signal was stored for off-line analysis with Clampex 9.0 software (Molecular Devices) or Pulse/Pulse fit v.8.74 (HEKA Elektronik) and IGOR Pro v.4.03 (WaveMetrics). Pipettes (4–8 MΩ) for whole cell recording were pulled on a horizontal micropipette puller (P-97, Sutter Instrument) from filamented capillary glass and were filled with a pipette solution containing (in mM) 125 CsMeSO4, 2 CsCl, 10 HEPES, 0.1 EGTA, 4 MgATP, 0.3 NaGTP, and 10 phosphocreatine, with 5 mM QX-314 (pH 7.4, adjusted with CsOH, 290–295 mosM). Membrane voltages were compensated for an estimated liquid junction potential of 10 mV. Cells requiring firing property characterization were recorded with a pipette solution containing (in mM) 130 potassium gluconate, 5 KCl, 2 MgCl2, 4 MgATP, 0.3 GTP, 10 phosphocreatine, and 10 HEPES (pH 7.3 with KOH). Neurons were given at least 5 min after gigahm seal formation and patch rupture to stabilize before data collection. Series resistance was compensated by 80% and was continually monitored throughout the experiment. Cells were discarded if the series resistance changed by >15%. We monitored the peak amplitude of a brief hyperpolarizing test pulse (10 ms, −5 mV) given after thalamic stimulation to ensure consistent series resistance during the entire experiment, and only recordings that remained stable over the period of data collection were used.

Auditory pyramidal neurons were held at −70 mV to record excitatory postsynaptic currents (EPSCs). Inhibitory inputs were blocked with the GABA_A-type receptor blocker bicuculline in some of the experiments. A Grass S88 stimulator (Astro-Medical, West Warwick, RI) and a constant-current stimulus isolation unit (Grass Instruments) were used to evoke EPSCs by stimulating the MGB. A bipolar stimulating electrode was used to deliver monophasic stimulus pulses (0.2 ms, at 0.05 Hz), and the stimulation intensity was adjusted to evoke EPSCs that were 30% of maximal evoked amplitudes. In control experiments, “baseline” EPSCs were recorded for 10 min at the test stimulation intensity. Long-term plasticity was induced by switching the amplifier to current-clamp mode and delivering four 1-s 100-Hz trains at 20-s intertrain intervals. The criteria that we used to obtain the percentage of neurons for different types of plasticity are as follows: 1) If the increase in EPSC amplitude to its maximum value is shorter than 5 min and then stabilizes or continues to increase 35 min after HFS, it is considered a short-lasting LTP. 2) If the increase in EPSC amplitude to its maximum value is longer than 5 min and then starts to return toward baseline within 35 min after HFS, it is considered a short-lasting LTD. 3) Similarly, we consider LTD that induces a quick decline to minimum EPSC amplitude within 5 min and then quick return toward the baseline to be a fast LTD. 4) We consider LTD that induces a gradual decrease in EPSC amplitude within 30 min, which then stabilizes, to be a slow LTD. When further pharmacological experiments were needed, neurons were always allowed to recover to 95% of their baseline level before exposure to pharmacological reagents. It usually took ~10 min to see a 95% recovery while cells were still in good condition.

GABAergic miniature inhibitory postsynaptic currents (mIPSCs) were recorded in the presence of ionotropic glutamate receptor blockers, including CNQX (20 μM) and APV (50 μM) in the superfusing ACSF. One micromolar tetrodotoxin (TTX) applied to the bath solution completely blocked voltage-dependent Na+ channels within 5 min. Neurons were voltage-clamped at +10 mV for mIPSC recording.

Recording of Receptive Field in Auditory Cortex

The protocols for acoustic stimulus and electrical stimulation in the MGB and auditory cortex have been provided in previous publications (Zhu et al. 2013). Briefly, the acoustic stimuli were a series of white noise or pure tone bursts at 5-ms rise/decay time for 60-ms duration. A multibarrel glass electrode with a carbon fiber in the central barrel was advanced to the right auditory cortex. Four surrounding barrels were connected to the Neuro Phore System (6400 Advanced, Dagan) for microiontophoretic injection of different receptor antagonists. Signals from the electrode were fed to a RA16PA multichannel preamplifier (Tucker-Davis Technologies) and filtered with a band pass of 0.3–10 kHz. Single units were isolated and analyzed with BrainWare software (Tucker-Davis Technologies). The excitatory responses of AC neurons to acoustic stimuli were first measured with the computer-controlled frequency/amplitude scan. The receptive fields (areas in which acoustic stimulation leads to a response in an AC or MGB neuron), frequency-threshold curves, and BF were subsequently derived from the collected data. HFS (four 1-s 100-Hz trains at 20-s intertrain intervals) was delivered to the tungsten electrode placed in the MGB. Changes in AC responses after electrical stimulation of the MGB were in the presence or absence of different receptor antagonists were recorded.

Anatomic Localization and Histology

Tract tracing with DiI. The fluorescent lipophilic tracer DiI was used to examine fiber pathways in recorded slices. The slices were fixed by immersion in 4% paraformaldehyde for 3 days. DiI was
delivered into the MGB, under a dissecting microscope with a broken micropipette. The slices were then placed in small plastic cups and covered in warm liquid agarose (3%) that was made with PBS containing 0.1% sodium azide. After the agarose solidified, the cups were filled to the top with PBS, sealed, and placed in the dark at 37°C for 1 mo to allow sufficient DiI diffusion to occur. The slices were subsequently sectioned on a vibratome at 50 μm. After three rinses with PBS, the slices were mounted on gelatin-coated slides and coverslipped.

**Pyramidal cell identification.** Biocytin hydrochloride was dissolved in the pipette solution in a number of recordings after the completion of data collection (final concentration: 0.5%) to identify auditory pyramidal cortical neurons. Slices with biocytin-filled cells were first transferred to 4% paraformaldehyde for 48 h and were then cryoprotected. The sections were incubated in avidin-biotin-HRP complex (ABC kit, Vector Labs) at 37°C for 3 h. They were then rinsed in a phosphate buffer and incubated with nickel/cobalt-intensified diaminobenzidine (DAB). The sections were then mounted and coverslipped. Neurons were visualized with a fluorescence microscope (Olympus, Tokyo, Japan).

**Drugs**

All reagents were obtained from Sigma-Aldrich, with the exception of QX-314 (Tocris, Ellisville, MO). Bicuculline and CNQX were dissolved in dimethyl sulfoxide. Other drugs were dissolved in ACSF. All drugs were prepared as concentrated stock solutions and were added immediately either to the recording ACSF or to the internal solution at working concentrations (1:1,000 dilution) and then frozen at −20°C until use.

**Statistical Analyses**

Data are presented as means ± SE. Statistical analysis was performed with a one-way analysis of variance (ANOVA) test with SPSS 18.0 software and Student’s t-test. Significance was set at the level of \( P < 0.05 \).

**RESULTS**

**HFS of MGB\(_v\), Induced Bidirectional Plasticity in Rat Auditory Cortex**

To determine the changes in synaptic plasticity in response to thalamic stimulation, we made whole cell patch-clamp recordings of EPSCs from thalamorecipient layer III/IV pyramidal neurons in a slice that contained auditory TC pathways. We first performed tract-tracing studies using the lipophilic dye DiI to ensure that the TC pathway in the slice was complete. We first performed tract-tracing studies using the lipophilic dye DiI to ensure that the TC pathway in the slice was complete. To determine the changes in synaptic plasticity in response to thalamic stimulation, we made whole cell patch-clamp recordings of EPSCs from thalamorecipient layer III/IV pyramidal neurons in a slice that contained auditory TC pathways. We first performed tract-tracing studies using the lipophilic dye DiI to ensure that the TC pathway in the slice was complete.

Figure 1A shows the results for a slice in which DiI was placed in the MGB\(_v\). The dye followed a pathway from the MGB\(_v\), toward projections along the medial edge of the lateral geniculate, after which it curved posterior-laterally around the hip- pocampus and moved toward the auditory cortex. On reaching the auditory cortical border, the fibers ascended to layers III–IV, where they formed a dense terminal plexus (Fig. 1B). We identified pyramidal AC neurons by their pyramidal-shaped cell bodies and long apical dendrites extending toward the pial surface (Fig. 1C), as described in previous reports (Rose and Metherate 2005). A subset of these cells were injected with biocytin for further morphological identification. All labeled cells had the morphological features of pyramidal neurons: a pyramidal soma and a prominent apical dendrite (Fig. 1D). Pyramidal cells are clearly identified by their relative broad spike width, slow spike afterhyperpolarization (AHP), low steady-state firing rate, and spike adaptation (Fig. 1, E and F, Table 1). After characterization of the intrinsic properties of the neurons, EPSCs were evoked by thalamic stimulation. Neurons were examined for each current level in steps of 50 μA. Figure 1G shows examples that were classified as presumed EPSCs of pyramidal cells. TC stimulation can reliably evoke EPSCs in layer III/IV pyramidal neurons (Fig. 1, G and H, Table 2).

After we identified pyramidal neurons, we conducted experiments to characterize the long-term synaptic plasticity of TC synapses that connect with regular spiking neurons in the auditory cortex. HFS (4 trains of 100 Hz for 1 s with an interval of 20 s) was applied to the layer when the amplitude of the EPSC was stable for >10 min. The amplitude of an individual EPSC was normalized to the averaged amplitude of the EPSCs that had occurred during the 10-min baseline recording. Our data showed that HFS of the MGB\(_v\), reliably induced five types of long-term plasticity at 218 of 249 (87.6%) of the thalamic inputs. Specifically, 21 TC inputs (8.4%) showed long-lasting LTP, 101 inputs (40.6%) showed short-lasting LTP, 24 inputs (9.6%) showed rapid LTD, 72 inputs (28.9%) showed slow LTD, and 31 inputs (12.5%) showed no change after stimulation (Fig. 2). Figure 2A shows the average time course of the EPSC amplitude changes induced by 21 long-lasting potentiation inputs. HFS initially elicited significant increase in the amplitude of EPSCs, which then plateaued. The normalized mean maximum EPSC amplitude increased to 210.4 ± 19.8% of the baseline (\( n = 21 \)). Representative traces in Fig. 2A, bottom, are averaged EPSCs from five consecutive responses taken before, immediately after, and 30 min after LTP induction. Figure 2B shows the time course of EPSC amplitude changes averaged from 101 short-lasting potentiation inputs. Potentiation of the EPSC amplitudes increased during the first 10 min after HFS and then returned gradually to the baseline. The mean maximum EPSC amplitude increased to 156.2 ± 24.5% of the baseline (\( n = 101 \)). Representative traces in Fig. 2B, top, are averaged EPSCs from 5 consecutive responses taken before, immediately after, 10 min after, and 30 min after LTP induction. Figure 2C shows the time course of EPSC amplitude changes averaged from 24 rapid depression inputs. HFS initially induced a significant decrease in EPSC amplitude and then stabilized. The mean minimum amplitude of the post-HFS EPSCs decreased to 99.0 ± 2.5% of the control (\( n = 24 \)). Figure 2D shows the time course of EPSC amplitude changes averaged from 72 slow depression inputs. EPSC amplitudes gradually decreased during the first 40 min after HFS and then stabilized. The mean minimum amplitude of the post-HFS EPSCs decreased to 65.2 ± 7.2% of the baseline (\( n = 72 \)). The remaining 31 of the 249 thalamic inputs (12.4%) did not change after HFS. The EPSC amplitudes for the inputs that did not show plasticity were stable throughout the testing period, and the mean post-HFS response amplitude was 99.0 ± 2.5% of the control (\( n = 31 \); Fig. 2E).

**Pharmacological Characteristics of Synaptic Plasticity Elicited by HFS of MGB\(_v\)**

We characterized these different forms of synaptic plasticity in the presence of different pharmacological agents. We first examined the involvement of \( N \)-methyl-d-aspartate (NMDA) receptors in thalamic HFS-induced long-lasting LTP. We recorded HFS of MGB\(_v\)-induced LTP prior to (as a control) and...
after application of D-APV (50 μM), a selective antagonist of the NMDA receptor. The mean maximum EPSC amplitude after HFS was 128.7 ± 13.6% of the baseline, and the mean EPSC amplitude 30 min after HFS was 101.7 ± 7.23% of baseline (n = 7; Fig. 3A). The long-lasting LTP was significantly suppressed in the presence of APV (P < 0.05, n = 7; Fig. 3B). We next examined whether the short-lasting LTP induced by thalamic stimulation relies on the activation of GABA<sub>A</sub> receptors, because activated AC neurons and stimulated MGB<sub>v</sub> neurons have been shown to drive IPSCs in AC neurons by activating interneurons (Xu et al. 2010). The GABA<sub>A</sub> antagonist bicuculline (10 μM) was applied in ACSF. Interestingly, bicuculline enhanced the magnitude of the short-lasting LTP that was obtained and turned short-lasting LTP into long-lasting LTP. For slices treated with bicuculline, the normalized mean maximum EPSC amplitude was 284.9 ± 22.1% of the baseline. The mean EPSC amplitude 30 min after the stimulation was 191.0 ± 27.6% of the baseline (n = 7; Fig. 3C). The magnitude of the LTP obtained in the presence of bicuculline was significantly larger than that of the control (P < 0.05, n = 7 for bicuculline, n = 20 for control; Fig. 3D). Similarly, bath application of D-APV (50 μM) also prevented the induction of short-lasting LTP (P < 0.05, n = 6 for APV, n = 20 for control; Fig. 3D). These results suggested that the induction of short-lasting LTP depends on the activation of both NMDA receptors and GABA<sub>A</sub> receptors. We then examined whether the activation of NMDA receptors is also necessary for the induction of rapid LTD. Our results showed that APV did not block induction of rapid LTD. The mean amplitude of EPSCs 30 min after HFS was 86.3 ± 8.7% of the baseline with APV and 82.7 ± 6.7% of the baseline without APV (n = 5; Fig. 4A). Previous studies have shown that some forms of the long-term plasticity of auditory TC synapses are metabotropic glutamate receptor dependent. In particular, type 5 metabotropic glutamate receptors (mGluR5) play an important role in modulating AC plasticity (Blundon et al. 2011;
of bicuculline, an antagonist of GABAA receptors, on slow LTD. Our results show that the slow LTD was almost completely suppressed by 5 µM bicuculline (n = 6; Fig. 5C), which suggests the involvement of GABAA receptors in slow LTD.

These experiments as a whole indicate that long-lasting LTD involves activation of NMDA receptors and short-lasting LTD involves activation of both NMDA and GABA_A receptors. Rapid LTD involves activation of both mGluR5 and eCB1Rs, and slow LTD involves activation of both NMDA and GABA_A receptors. A summary showing the four types of plasticity and their pharmacological profiles is provided in Table 3.

**Table 1. Summary of type-dependent neuronal intrinsic properties**

<table>
<thead>
<tr>
<th></th>
<th>LTP_long</th>
<th>LTP_short</th>
<th>LTD_r</th>
<th>LTD_s</th>
<th>NC</th>
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<tr>
<td>n</td>
<td>7</td>
<td>20</td>
<td>8</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>R_m, MΩ*</td>
<td>244.10 ± 7.66</td>
<td>262.06 ± 8.02</td>
<td>188.83 ± 6.83</td>
<td>201.06 ± 7.72</td>
<td>292.65 ± 8.26</td>
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<tr>
<td>V_th, mV*</td>
<td>−37.81 ± 0.76</td>
<td>−44.63 ± 0.49</td>
<td>−37.78 ± 0.61</td>
<td>−27.53 ± 0.52</td>
<td>−35.42 ± 0.69</td>
</tr>
<tr>
<td>RMP, mV</td>
<td>−58.23 ± 0.65</td>
<td>−63.53 ± 0.72</td>
<td>−67.09 ± 0.79</td>
<td>−63.68 ± 0.61</td>
<td>−58.85 ± 0.68</td>
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<tr>
<td>AP amp, mV</td>
<td>108.40 ± 0.53</td>
<td>107.58 ± 0.46</td>
<td>117.06 ± 0.61</td>
<td>112.86 ± 0.69</td>
<td>118.21 ± 0.73</td>
</tr>
<tr>
<td>AP width, ms*</td>
<td>0.61 ± 0.04</td>
<td>0.29 ± 0.08</td>
<td>0.55 ± 0.06</td>
<td>0.42 ± 0.04</td>
<td>0.49 ± 0.09</td>
</tr>
<tr>
<td>Max rate, Hz*</td>
<td>109.29 ± 1.53</td>
<td>78.74 ± 1.51</td>
<td>109.28 ± 2.68</td>
<td>125.78 ± 1.34</td>
<td>87.7 ± 1.32</td>
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</table>

Values are means ± SE for n cells sampled. LTP_long, long-lasting long-term potentiation; LTP_short, short-lasting LTD; LTD_r, rapid long-term depression; LTD_s, slow LTD; NC, no change; R_m, input resistance; V_th, voltage threshold to spike; RMP, resting membrane potential; AP amp, action potential amplitude; AP width, action potential half-width; adaptation ratio, average of the last 2 interspike intervals (ISIs) divided by the average of the first 2 ISIs; Max rate, maximum spike rate evoked by ±300-pA current injection. *P < 0.05 (1-way ANOVA).

Kudoh et al. (2002). We therefore examined the involvement of mGlur5 in rapid LTD and found that bath application of the selective mGlur5 antagonist MPEP (10 µM) significantly inhibited rapid LTD. The mean amplitude of EPSCs 30 min after HFS was 92.5 ± 8.7% of the baseline with MPEP and 66.0 ± 9.9% of the baseline without MPEP (P < 0.05, n = 5; Fig. 4B).

We explored the role of eCB type I receptors (eCB1Rs) in rapid LTD by examining the effects of the eCB1R antagonist AM251 because previous studies have indicated that eCBs, the endogenous ligands for cannabinoid receptors, play a role in mGlur5-dependent LTD (Freund et al. 2003). We found that AM251 at 10 µM also blocked rapid LTD. The mean amplitude of EPSCs 30 min after HFS was 93.3 ± 8.7% of the baseline with AM251 and 79.5 ± 11.5% of the baseline without AM251 (P < 0.05, n = 4; Fig. 4C). The histogram of minimum amplitudes of EPSCs in Fig. 4D indicates that rapid LTD may be mGlur5 (P < 0.05, n = 5) and eCB1R (P < 0.05, n = 4) dependent. Finally, we examined the possible roles of glutamatergic and GABAergic receptors in slow LTD. The mean minimum amplitude of EPSCs 30 min after HFS was 78.4 ± 7.1% of the baseline with APV and 56.6 ± 7.4% of the baseline without APV (n = 7; Fig. 5A). We found that the slow LTD was suppressed significantly (P < 0.05, n = 7; Fig. 5D) in the presence of 50 µM APV. However, the selective mGlur antagonist MPEP (10 µM) had no significant effect on slow LTD (P = 0.72, n = 6; Fig. 5D). The mean minimum amplitude of the EPSCs 30 min after HFS was 59.7 ± 8.3% of baseline with MPEP and 58.5 ± 7.1% of the baseline without MPEP (n = 6; Fig. 5B). Finally, we investigated the effects of bicuculline, an antagonist of GABA_A receptors, on slow LTD. Our results show that the slow LTD was almost completely suppressed by 5 µM bicuculline (n = 6; Fig. 5C), which suggests the involvement of GABA_A receptors in slow LTD.

**Table 2. Summary of type-dependent synaptic properties**

<table>
<thead>
<tr>
<th></th>
<th>LTP_long</th>
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<td>n</td>
<td>7</td>
<td>20</td>
<td>8</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Average onset latency, ms*</td>
<td>3.96 ± 0.31</td>
<td>7.01 ± 0.43</td>
<td>7.86 ± 0.52</td>
<td>6.81 ± 0.40</td>
<td>7.63 ± 0.55</td>
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<tr>
<td>Onset latency variability jitter*</td>
<td>0.38 ± 0.12</td>
<td>0.55 ± 0.11</td>
<td>0.51 ± 0.13</td>
<td>0.73 ± 0.16</td>
<td>0.83 ± 0.12</td>
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<td>Amplitude, pA*</td>
<td>−47.36 ± 0.55</td>
<td>−78.07 ± 1.08</td>
<td>−62.06 ± 0.79</td>
<td>−105.23 ± 0.81</td>
<td>−21.73 ± 0.48</td>
</tr>
<tr>
<td>Rise time, 20–80%, ms*</td>
<td>2.61 ± 0.11</td>
<td>5.06 ± 0.21</td>
<td>2.97 ± 0.61</td>
<td>3.03 ± 0.16</td>
<td>4.08 ± 0.66</td>
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<tr>
<td>Width, ms*</td>
<td>38.12 ± 2.40</td>
<td>41.58 ± 3.31</td>
<td>38.33 ± 2.71</td>
<td>32.88 ± 2.63</td>
<td>42.92 ± 5.60</td>
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Values are means ± SE for n cells sampled. *P < 0.05 (1-way ANOVA).

**Inhibition of Glutamate and GABA_A Receptors Prevents MGB_β, Activation-Induced BF Shift in AC Neurons**

We next asked whether these forms of TC synaptic plasticity and their responsible receptors could contribute to MGB_β, stimulation-induced shift of BF in the auditory cortex, as demonstrated by our recent in vivo studies using anesthetized rats (Zhu et al. 2013). To answer this question, we examined the changes in the frequency-tuning curve of AC neurons before and after blockade of glutamate and GABA_A receptors (see MATERIALS AND METHODS). In Fig. 6A, a cortical neuron was tuned to 23.0 kHz. When the thalamic neuron was electrically stimulated, the frequency-tuning curve of the cortical neuron sharply tuned to 21.0 kHz. The shifted BF returned to the control BF ~90 min after the stimulation.

Application of APV to AC neurons before the stimulation reduced the shift of BF by 10.22 ± 0.32 kHz on November 2, 2016 http://jn.physiology.org/ Downloaded from
application of bicuculline and MPEP abolished the BF shift after the onset of MGBv activation (Fig. 6E). In six cortical neurons studied, the BF shift was significantly smaller than that without bicuculline and MPEP (P < 0.05, n = 6; Fig. 6F). These experiments indicate that application of APV, MPEP, and bicuculline to AC neurons can inhibit the shift in cortical BF induced by HFS of the MGBv. These data further support essential roles for these receptors and TC synaptic plasticity in frequency-specific plasticity of the rat auditory cortex.

**Thalamic Activation May Induce Inhibitory Potentiation in Auditory Cortex by Acting on Presynaptic Sites**

Our study underscores the important roles of not only the well-known excitatory glutamate but also the inhibitory GABA in thalamic activation-mediated frequency-specific cortical plasticity. These data and other evidence accumulated in recent years strongly support the hypothesis that inhibitory plasticity participates in most AC computations (Collingridge et al. 2004; Xu et al. 2010). Despite the advances in our understanding of glutamate transmission and receptor functions in mediating long-term cortical plasticity, neither the role nor the precise synaptic (pre- compared with postsynaptic) mechanism of GABA-mediated plasticity is well known. We therefore next investigated whether presynaptic transmitter release and/or postsynaptic receptor responsiveness was enhanced at GABAAergic synapses of AC neurons after thalamic HFS. mIPSCs in pyramidal cortical neurons were therefore recorded in the presence of TTX. A stable baseline of mIPSCS was first recorded for 5 min as a control, followed by a period of TTX washout for 15 min. HFS was then applied to the MGBv and TTX was subsequently washed in (Fig. 7A). To record mIPSCs, pyramidal cells were voltage-clamped at -10 mV and ionotropic glutamate receptor-induced spontaneous EPSCs were blocked with CNQX (10 μM) and APV (50 μM) in ACSF. Under these experimental conditions, mIPSCs were recorded as outward currents (Fig. 7B). These events were blocked by 10 μM bicuculline (data not shown), which indicates that they are mediated by the release of GABA. The frequency of mIPSCs 25–30 min after HFS was significantly increased in thalamorecipient pyramidal neurons of the auditory cortex (from 40.33 ± 4.49 to 89.65 ± 6.53 events in 1 min, n = 6, P < 0.05; Fig. 7, B–D). The amplitude of the mIPSCs was not altered after conditioning HFS (baseline 85.38 ± 7.08 pA compared with 90.16 ± 8.12 pA at 25–30 min after HFS, P > 0.05; Fig. 7, B–D). Neither the frequency nor the amplitude of mIPSCs was affected in three neurons that did not receive thalamic input from the MGBv (data not shown). A change in the frequency of spontaneous postsynaptic current indicates a presynaptic mechanism, whereas a change in spontaneous postsynaptic current amplitude indicates a change in postsynaptic responsiveness (Van der Kloot 1991). These data suggest that the MGBv, activation-mediated facilitation of the GABAAergic synaptic transmission may occur at the presynaptic site.
DISCUSSION

The frequency-specific plasticity of AC neurons induced by MGBb activation has been studied in mice and bats, but the underlying cellular mechanisms are not well understood. Our present study of MGBv activation-mediated long-term plasticity in the rat auditory cortex demonstrates that different forms of long-term plasticity of TC inputs depend on the activation of different sets of ionotropic and metabotropic glutamate receptors, GABA\(_A\) receptors, and eCB receptors and that MGBv activation induces an enhancement of GABAergic synaptic transmission that involves presynaptic mechanisms.
Long-Lasting LTP May Represent Monosynaptic Potentiation After Thalamic HFS

In the present study, NMDA receptor-dependent rapid and long-lasting LTP was elicited in rat AC neurons after HFS of the MGBv (Fig. 3A). Similarly, NMDA receptor-dependent LTP has been found in the mouse auditory cortex (Liu et al. 2013). Because thalamorecipient neurons in the cortex are interconnected, stimulation of TC afferents may polysynaptically activate intracortical feedforward excitatory synapses (Blundon et al. 2011; Speechley et al. 2007). It is unclear which specific synaptic pathway showed rapid LTP after HFS of the MGBv. The short onset latency response and low jitter of onset latency are two principal criteria to identify monosynaptic TC EPSC (Cruikshank et al. 2002; Rose and Metherate 2005). Our study demonstrates that thalamic stimulation-evoked EPSCs had a short onset latency of 3.96 ± 0.31 ms and little onset latency jitter (0.38 ± 0.12 ms) in the inputs that expressed rapid and long-lasting LTP. These EPSCs exhibited little change in latency with increased stimulus intensity and fixed latencies with high-frequency repetitive stimulation, which suggests activation of monosynaptic TC connections (Table 2). We thus assume that the rapid and long-lasting LTP in the present study results from monosynaptic TC inputs that are based on an NMDA receptor-dependent mechanism.

Short-Lasting LTP May Represent Polysynaptic Potentiation After Thalamic HFS

In the present study, the EPSCs evoked in the inputs that showed short-lasting LTP had long latencies and high variability jitter (Table 2), suggesting the activation of polysynaptic connections (Berry and Pentreath 1976; Blundon et al. 2011; Cruikshank et al. 2002; Rose and Metherate 2005; Speechley et al. 2007). In addition, the sensitivity of short-lasting LTP to antagonists of both NMDA and GABAergic receptors indicated that pyramidal neurons in the auditory cortex receive both glutamatergic inputs and GABAergic inputs from interneurons (Fig. 3C). Previous studies have reported that the presence of GABAergic interneurons may contribute to the induction of short-lasting LTP (Chapman et al. 1998; Grover and Yan 1999). Our data show that the blockage of GABA_A receptors facilitates the induction of NMDA receptor-dependent short-lasting LTP. We therefore speculate that synapses that ex-

Table 3. Summary of four types of plasticity and their pharmacological profiles

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LTP_long</th>
<th>LTP_short</th>
<th>LTD_s</th>
<th>LTD_d</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Amplitude*</td>
<td>2.43 ± 0.32</td>
<td>1.77 ± 0.30</td>
<td>0.44 ± 0.08</td>
<td>0.63 ± 0.12</td>
</tr>
<tr>
<td>Slope*</td>
<td>4.29 ± 0.30</td>
<td>0.35 ± 0.32</td>
<td>1.81 ± 0.1</td>
<td>0.01 ± 0</td>
</tr>
<tr>
<td>Recovery time, min</td>
<td>22.12 ± 3.08</td>
<td>25.03 ± 4.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacological profile</td>
<td>APV+</td>
<td>APV+</td>
<td>MPEP+</td>
<td>APV+</td>
</tr>
</tbody>
</table>

Parameter values are means ± SE for n cells sampled. Amplitude, amplitude of LTP (LTD); slope, slope of LTP (LTD) as measured at half-amplitude of LTP (LTD); recovery time, time required for excitatory postsynaptic current (EPSC) to recover from LTD/LTP to 85% of its amplitude; + , had an effect on LTP (LTD); − , had no effect on LTP (LTD); BIC, bicuculline. *P < 0.05 (1-way ANOVA).
hibit short-lasting LTP receive either more synaptic inhibition or less excitatory drive and therefore have a high threshold for producing LTP. Interestingly, our experiments show that short-lasting LTP depends on both NMDA and GABAA receptors. However, the induction of long-lasting and short-lasting LTP in the hippocampus and visual cortex also depends on different NMDA receptor subtypes (Castro-Alamancos and Connors 1996; Volianskis et al. 2013). In the future, it will be interesting to investigate whether different subtypes of NMDA receptors are present that

Fig. 6. Blockade of glutamate and GABAergic receptors inhibited best frequency (BF) shifts of cortical neurons evoked by HFS of the MGBv. A: HFS of the MGBv evoked a BF shift [electrical stimulation (ES)] of an auditory cortical (AC) neuron. B: 0.05 μl of 10 mM APV (pH 7.0; dissolved in 0.9% saline) applied to auditory cortex reduced the responses and inhibited BF shifts of the cortical neuron. C: changes in the BF shift after HFS of the MGBv in the absence (control) or presence of APV. *P < 0.05, n = 7. D: HFS of the MGBv evoked a BF shift (ES) of an AC neuron. E: 0.05 μl of 1 μM BIC and 0.5 μM MPEP (pH 7.0; dissolved in 0.9% saline) applied to auditory cortex increased the responses and inhibited BF shifts of the cortical neuron. F: changes in BF shift after HFS of the MGBv in the absence (control) or presence of BIC and MPEP. *P < 0.05, n = 6.

Fig. 7. HFS of the MGBv increased the frequency but not the amplitude of miniature inhibitory postsynaptic current (mIPSC) in AC neurons. A: experimental design for the recording of mIPSCs. B: representative example of mIPSCs recorded from an AC neuron that received synaptic input from the MGBv under baseline conditions and 25–30 min after HFS. Calibration: 200 ms, 50 pA. C: cumulative probability curve of interevent intervals (left) for mIPSCs from the neuron shown in A was shifted 25–30 min after HFS compared with baseline, which indicates enhanced transmitter release. In contrast, no change in the cumulative probability curve of amplitudes (right) of mIPSCs was observed. A total of 70 events for baseline and 200 events that occurred at 25–30 min after HFS were plotted. D: summary of the change in frequency and amplitude of mIPSCs from 10 thalamorecipient AC neurons. *P < 0.05; n.s., not significant (P > 0.05).
might contribute to the induction of short-lasting LTP in our model.

Rapid LTD May Represent eCBR-Dependent mGluR-Dependent LTD

In the present study we found that the rapid LTD following HFS of the MGBv was dependent on the activation of mGluR5 but not of ionotropic NMDA receptors (Fig. 4). Several previous studies have also shown the importance of mGluR-dependent LTD in the auditory cortex, visual cortex, striatum, cerebellum, and hippocampus (Blundon et al. 2011; Calabresi et al. 1992; Kudoh et al. 2002; Luscher and Huber 2010). Studies have further demonstrated that mGluR-initiated LTD involves the activity of a retrograde messenger, the eCB, that is synthesized and released from a postsynaptic cell by the activation of mGluRs (Gerderman and Lovinger 2003). Upon release, eCBs act presynaptically to regulate the probability of glutamate release and to alter release mechanisms after mGluR stimulation (Grueter et al. 2007). On the basis of these and our present findings, we speculate that HFS of the MGBv led to the sequential activation of mGluR5 in pyramidal neurons and the activation triggered the release of neuromodulators such as eCBs (Freund et al. 2003; Huang et al. 2008). The eCBs in turn activated receptors in those distant stimulated or nonstimulated synapses, and the synaptic transmission in those synapses was inhibited, leading to rapid LTD (Serrano et al. 2006).

Slow LTD May Represent Thalamocortical Polysynaptic Depression After Thalamic HFS

APV, but not MPEP, effectively blocked the induction of slow LTD in the present study (Fig. 5, A and B), which indicates that NMDA receptors play an important role in the induction of slow LTD. Interestingly, our data further demonstrate that slow LTD was also suppressed significantly by bicuculline, which indicates the involvement of GABA_A receptors (Fig. 5C). Similar involvement of GABA receptor activity has been found in the mouse auditory cortex (Liu et al. 2013). Previous reports have shown that the inhibition level mediated by GABA receptors determines the direction of synaptic plasticity during HFS-induced LTD in the neocortex by modulating postsynaptic depolarization (Artola et al. 1990). Low levels of postsynaptic depolarization lead to LTD, whereas stronger depolarization leads to LTP (Artola et al. 1990; Ngezahayo et al. 2000). Our overall conclusion is that synapses in pyramidal neurons are activated when HFS is applied to the MGBv. However, inhibitory interneurons were also driven by axon collaterals of MGBv neurons or by activated AC neurons (Fig. 7). HFS may provide an optimal depolarization level for LTD induction by concurrently activating GABAergic and glutamatergic transmission. It is therefore not surprising that HFS of the MGBv can induce a slow type of LTD in AC neurons.

A Possible Synaptic Mechanism Underlying MGBv Stimulation-Induced Auditory Plasticity

Serial section reconstruction of single MGBv axon in the auditory cortex revealed that a single MGBv axon may project onto many AC neurons, and a single neuron in the auditory cortex may receive inputs from a large number of thalamic neurons (Cetas et al. 1999; de Venecia and McMullen 1994; Hashikawa et al. 1995). Paired recordings of neurons in the MGB, and the auditory cortex reveal that TC projections link MGB, and AC neurons with similar BF (Miller et al. 2001). There are also abundant cortico-cortical connections within the auditory cortex (McMullen and de Venecia 1993). In the present study, cells that expressed long-lasting LTD are clearly differentiated from other cells by their low thresholds, adaptation ratio, and maximum firing rates, as well as their large and broad EPSCs. Conversely, cells that expressed slow LTD are characterized by their high thresholds, broad spikes, as well as large and narrow EPSCs (Tables 1 and 2). These differences between the plasticity classes in both intrinsic and synaptic properties suggest that they may represent a separate class of neurons or receive a separate class of synaptic inputs. On the basis of previous findings that AC receptive field plasticity is highly frequency specific (Weinberger 2007; Zhu et al. 2013) together with the present data showing the importance of inhibitory and excitatory synaptic transmission in AC frequency-specific plasticity (Fig. 6), we developed a possible AC synaptic mechanism model for frequency-specific AC plasticity that is induced by focal thalamic stimulation.

Specifically, in Fig. 8A, AC neuron A2 receives excitatory TC inputs from thalamic neuron M2, which has the same BF as A2, and A2 also receives collateral projection inputs from such other thalamic neurons as M1 and M3, which have BFs that differ from that of A2. In addition to the TC inputs, pyramidal neurons in the auditory cortex also receive excitatory inputs from other glutamatergic pyramidal neurons, such as A1 and A3, and inhibitory inputs from GABAergic interneurons, such as I1 and I2.

If A2 has the same BF as the stimulated M2, the TC synapse between M2 and A2 will show NMDA receptor-dependent LTD after activation of M2 by focal HFS (Fig. 8A, Fig. 3A). Enhancements of the excitatory postsynaptic potential trigger an increase of A2’s response to tone. If, on the other hand, the BF of the recorded AC neuron is different from the BF of the stimulated MGBv neuron, the underlying synaptic mechanism is more complex. We stimulated M1 in the MGBv and recorded the activity of neuron A2 in the auditory cortex (Fig. 8A). After HFS, synapses of collateral projections from M1 to A2 showed NMDA-dependent LTD. The facilitated cortical neuron A1 may also enhance the responses of A2 through intracortical excitatory projections. These two mechanisms cause the recorded AC neuron to show facilitation at or near the BF of the stimulated thalamic neuron. We hypothesize that there are two possible reasons for inhibition at or near the BF of the recorded AC neuron. First, stimulated MGBv neurons and facilitated AC neurons can decrease the responses of AC neurons through inhibitory interneurons. As shown in Fig. 8A, the inhibitory interneuron I1 was also driven by axon collaterals from M1 or A1 when focal HFS was applied to the thalamic neuron M1. The action of interneuron I1 produced membrane hyperpolarization of A2. Synapses from M2 to A2 may be activated by the limited spread of electrical stimulation. HFS may provide an optimal depolarization level for LTD induction by concurrently activating GABAergic and glutamatergic transmission. A second possibility is that heterosynaptic suppression is involved in the inhibition. As shown in Fig. 8C, HFS leads to glutamate release, which triggers NMDA-dependent LTD in the
activated synapse. Glutamate triggers a simultaneous heterosynaptic depression (Fig. 8C).

Every neuron in the neocortex has thousands of synapses. Activation of only a few hundred of these synapses can evoke cell firing (Crochet et al. 2005). As shown in Fig. 8B, neuron A2 in layers III/IV of the auditory cortex has thousands of synapses. A tone at a frequency within the receptive field of A2 might activate only a portion of these synapses. Another tone at a different frequency can activate another group of these synapses. These synapses may show different forms of long-term plasticity after focal thalamic HFS. Changes in postsynaptic potential that respond to a certain frequency should be the summation of the LTP and LTD that are mediated by that set of activated synapses at the frequency. The summative change in postsynaptic potential in response to a certain frequency may therefore be LTP, LTD, or no change (Fig. 8B, top).

However, one would need to be aware that the excitability of stimulated neurons can additionally be modified by conditional stimulation. Bidirectional changes in the intrinsic excitability of CA1 hippocampal pyramidal neurons are often observed after induction of synaptic LTP or LTD (Li et al. 2004). It is possible that the intrinsic excitability of the stimulated MGBv neurons is modified by HFS, which in turn affects the auditory synaptic plasticity. Future studies will be required to investigate these possibilities.

In addition, previous studies have revealed neuronal plasticity in the auditory cortex in both awake and behaving animals of different species (Banerjee and Liu 2013; David et al. 2012; Guo et al. 2013; Jaramillo and Zador 2011). A very recent study also confirmed that in mice under anesthesia the LTP and LTD induced by thalamic stimulation can contribute to the remodeling of receptive fields in the auditory cortex (Liu et al. 2013). Our results further demonstrated that the plasticity evoked by repetitive thalamic stimulation could be generated through a fundamental TC circuit alone without inputs from other sources. Other factors like attention or cross-modality effect in awake animals may modulate the characteristics of neuronal plasticity generated by this TC pathway through different mechanisms.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: Z.z. and X.Y. conception and design of research; Z.z., X.F., and Z.J. edited and revised manuscript; Z.z., X.F., and Z.J. performed experiments; Z.z., X.F., and H.b. analyzed data; Z.z. and C.p. prepared figures; Z.z. and X.F. drafted manuscript; Z.z., X.F., C.p., M.Z., and Z.J. edited and revised manuscript; Z.z., X.F., and Z.J.

Fig. 8. Hypothetical model for illustrating the role of the TC system in frequency-specific plasticity of AC neurons. A: AC neuron A2 receives TC inputs from M2, which has the same BF as A2. A2 also receives TC inputs from MGBv neurons that have BFs differing from those of A2, such as M1 and M3. In addition to the TC inputs, A2 receives excitatory intracortical inputs from other AC neurons, such as consecutive A1 and A3. In addition, A2 also receives inputs from such GABAergic inhibitory interneurons as I1 and I2. Spectral information therefore converges on A2 by the means of a combination of TC and intracortical pathways. B: amplification of neuron A2 (dashed box in A) to show the distribution of its synapses. A2 receives impulses from thousands of synapses, and a given frequency activates only a portion of these synapses. Activation of this portion of synapses causes neuron A2 to fire. Another frequency in the receptive field can activate a different portion of synapses to A2. Different forms of changes in synaptic transmission in A2 can be induced by HFS of the MGBv. Changes in postsynaptic potential to a certain stimulus frequency should be a summation of LTP and LTD that are mediated by that set of synapses activated by the frequency. C: simplified schematic diagram for long-lasting changes of synaptic transmission. Left: a condition where one of the synapses is activated by HFS. HFS leads to the release of presynaptic vesicles containing glutamate (Glu) that activate NMDA receptors, which results in a potentiation of this activated synapse. Postsynaptic depolarization that is induced by HFS is small in some cases because of the inhibition exerted by interneurons. Right: Glu simultaneously triggers heterosynaptic depression. This begins with the activation of an mGlu5 receptor, which then triggers a greater release of a neuromodulator (indicated by green circles). This modulator can diffuse and activate its receptors in distal nonactivated synapses, which depresses the target synapse.
approved final version of manuscript; X.F., J.W., C.p., H.b., and X.Y. interpreted results of experiments.

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